



Clinical trial results:

A Randomized, Single-blind, Dose-Ranging Study to Evaluate Immunogenicity, Safety and Tolerability of Different Formulations of Adjuvanted and non-Adjuvanted Egg-derived, Inactivated Novel Swine Origin A/H1N1 Monovalent Subunit Influenza Virus Vaccine in Healthy Subjects from 6 Months to 17 Years of Age

Summary

EudraCT number	2009-013672-45
Trial protocol	NL DE BE
Global end of trial date	01 July 2011

Results information

Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	07 January 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Required for the re-QC project because of the EudraCT system glitch and possible updates to results may be required. Moreover, a change in system user for this study is necessary.

Trial information

Trial identification

Sponsor protocol code	V111_03
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00971542
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l
Sponsor organisation address	Via Fiorentina 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines , RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines , RegistryContactVaccinesUS@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000599-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
--	-----

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 October 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify the preferred vaccine formulation (with and without MF59), dosage (of antigen and adjuvant) and schedule (one or two administrations) of the egg-derived H1N1sw monovalent vaccine in healthy adults based on CHMP criteria and pairwise statistical comparisons for immunogenicity, and safety & tolerability.

Protection of trial subjects:

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines.

An oral temperature $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$) or serious active infection was a reason for delaying vaccination.

Standard immunization practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine is not injected into a blood vessel.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason, Scientific research
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Belgium: 201
Country: Number of subjects enrolled	Germany: 178
Country: Number of subjects enrolled	Chile: 208
Country: Number of subjects enrolled	Dominican Republic: 66
Worldwide total number of subjects	684
EEA total number of subjects	410

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	236
Children (2-11 years)	353
Adolescents (12-17 years)	95
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from ten sites in Germany, two sites in Belgium, one site in the Netherlands, two sites in the Dominican Republic, two sites in Chile.

Pre-assignment

Screening details:

All subjects enrolled were included in the trial.

Period 1

Period 1 title	Per arm in the overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (3.75_Half MF59)

Arm description:

Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25mLdoses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM.

Arm title	Cohort 1 (7.5_Full MF59)
------------------	--------------------------

Arm description:

Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5mLdoses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM.

Arm title	Cohort 2 (3.75_Half MF59)
------------------	---------------------------

Arm description:

Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25mLdoses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM.

Arm title	Cohort 2 (7.5_Full MF59)
------------------	--------------------------

Arm description:

Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5mL doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster seasonal vaccination with aTIV; all injections were administered IM

Arm title	Cohort 2 (15_No MF59)
------------------	-----------------------

Arm description:

Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (15mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	15_no MF59
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5mLdoses of H1N1 vaccine administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM

Arm title	Cohort 3 (3.75_Half MF59)
------------------	---------------------------

Arm description:

Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25mLdoses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM.

Arm title	Cohort 3 (7.5Full MF59)
------------------	-------------------------

Arm description:

Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5mLdoses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM.

Arm title	Cohort 3 (15_No MF59)
------------------	-----------------------

Arm description:

Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (1.5mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	15_no MF59
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5mLdoses of H1N1 vaccine (15mcg HA + no MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM

Arm title	Cohort 4 (3.75_Half MF59)
------------------	---------------------------

Arm description:

Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25mLdoses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart followed by one dose of 0.25mL booster vaccination with aTIV; all injections were administered IM.

Arm title	Cohort 4 (7.5_Full MF59)
------------------	--------------------------

Arm description:

Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	Focetria
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5mLdoses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart followed by one dose of 0.25mL booster vaccination with aTIV; all injections were administered IM.

Number of subjects in period 1	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Started	79	80	78
Completed	26	27	48
Not completed	53	53	30
Consent withdrawn by subject	6	6	7
Adverse Event	-	-	-
Administrative Reason	43	43	19
Adverse Events	-	-	-
Lost to follow-up	3	3	3
Unable to Classify	-	-	-
Protocol deviation	1	1	1

Number of subjects in period 1	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Started	78	39	75
Completed	51	25	52
Not completed	27	14	23
Consent withdrawn by subject	5	6	10
Adverse Event	-	-	1
Administrative Reason	20	8	3
Adverse Events	-	-	-
Lost to follow-up	2	-	8
Unable to Classify	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Started	73	37	72
Completed	57	28	47
Not completed	16	9	25
Consent withdrawn by subject	10	2	4
Adverse Event	-	-	-
Administrative Reason	2	1	6
Adverse Events	-	-	2
Lost to follow-up	4	3	2
Unable to Classify	-	3	11
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort 4 (7.5_Full MF59)
Started	73

Completed	47
Not completed	26
Consent withdrawn by subject	11
Adverse Event	-
Administrative Reason	5
Adverse Events	1
Lost to follow-up	1
Unable to Classify	7
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1 (3.75_Half MF59)
Reporting group description: Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).	
Reporting group title	Cohort 1 (7.5_Full MF59)
Reporting group description: Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).	
Reporting group title	Cohort 2 (3.75_Half MF59)
Reporting group description: Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (7.5_Full MF59)
Reporting group description: Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (15_No MF59)
Reporting group description: Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (15mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (3.75_Half MF59)
Reporting group description: Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (7.5Full MF59)
Reporting group description: Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (15_No MF59)
Reporting group description: Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (1.5mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (3.75_Half MF59)
Reporting group description: Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (7.5_Full MF59)
Reporting group description: Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	

Reporting group values	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Number of subjects	79	80	78
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: months arithmetic mean standard deviation	155.3 ± 30.6	156.4 ± 29.1	69.4 ± 21.3
Gender categorical Units: Subjects			
Female	38	39	39
Male	41	41	39

Reporting group values	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Number of subjects	78	39	75
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: months arithmetic mean standard deviation	71.8 ± 19.7	67.3 ± 21.2	24 ± 7.4
Gender categorical Units: Subjects			
Female	44	14	40
Male	34	25	35

Reporting group values	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Number of subjects	73	37	72
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years)			

Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: months			
arithmetic mean	23.9	25.1	8.8
standard deviation	± 6.4	± 6.4	± 1.3
Gender categorical			
Units: Subjects			
Female	42	17	36
Male	31	20	36

Reporting group values	Cohort 4 (7.5_Full MF59)	Total	
Number of subjects	73	684	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: months			
arithmetic mean	8.3		
standard deviation	± 1.4	-	
Gender categorical			
Units: Subjects			
Female	35	344	
Male	38	340	

End points

End points reporting groups

Reporting group title	Cohort 1 (3.75_Half MF59)
Reporting group description: Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).	
Reporting group title	Cohort 1 (7.5_Full MF59)
Reporting group description: Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).	
Reporting group title	Cohort 2 (3.75_Half MF59)
Reporting group description: Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (7.5_Full MF59)
Reporting group description: Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (15_No MF59)
Reporting group description: Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (15mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (3.75_Half MF59)
Reporting group description: Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (7.5Full MF59)
Reporting group description: Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (15_No MF59)
Reporting group description: Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (1.5mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (3.75_Half MF59)
Reporting group description: Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (7.5_Full MF59)
Reporting group description: Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Subject analysis set title	Per protocol set- Day 43 All Cohorts (3.75_Half MF59)
Subject analysis set type	Per protocol
Subject analysis set description: All subjects who received all the relevant doses of vaccine correctly and provided evaluable serum samples at relevant time points (day 43) and who had no major protocol violations as pre-specified in the analysis plan	
Subject analysis set title	Per protocol set- Day 43 All Cohorts (7.5_Full MF59)
Subject analysis set type	Per protocol
Subject analysis set description: All subjects who received all the relevant doses of vaccine correctly and provided evaluable serum	

samples at relevant time points (day 43) and who had no major protocol violations as pre-specified in the analysis plan

Subject analysis set title	Per Protocol Set-Day 43 ALL Cohorts (15_No MF59)
----------------------------	--

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

All subjects who received all the relevant doses of vaccine correctly and provided evaluable serum samples at relevant time points (day 43) and who had no major protocol violations as pre-specified in the analysis plan

Primary: Percentage of subjects achieving seroconversion against A/H1N1 Strain as measured by hemagglutination inhibition assay

End point title	Percentage of subjects achieving seroconversion against A/H1N1 Strain as measured by hemagglutination inhibition assay
-----------------	--

End point description:

1) Immunogenicity was measured in terms of percentage of subjects achieving seroconversion or significant increase in HI titer against the vaccine strain, weeks after receiving 2 doses of vaccination according to CHMP criterion.

2) Seroconversion is defined as HI $\geq 1:40$ for subjects negative at baseline (day 1) [$< 1:10$]; a minimum 4-fold increase in HI titer for subjects positive at baseline (day 1) [$HI \geq 1:10$] on Day 22, Day 43, Day 366 and Day 387 and percentage of subjects achieving seroconversion on Day 387 referring to pre-booster values.

3) There are no predefined CHMP criteria for the pediatric population however, the criterion is met if the percentage of subjects achieving seroconversion or atleast 4-fold increase in HI antibody (at day 43) is $> 40\%$.

End point type	Primary
----------------	---------

End point timeframe:

Day 43

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	70	66	60
Units: Percentages of subjects				
number (confidence interval 95%)	92 (83 to 97)	94 (86 to 98)	97 (89 to 100)	98 (91 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half)	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	60	58	31
Units: Percentages of subjects				
number (confidence interval 95%)	85 (69 to 95)	100 (94 to 100)	100 (94 to 100)	74 (55 to 88)

End point values	Cohort 4 (3.75_Half)	Cohort 4 (7.5_Full)		
------------------	-------------------------	------------------------	--	--

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: Percentages of subjects				
number (confidence interval 95%)	96 (87 to 100)	98 (89 to 100)		

Statistical analyses

Statistical analysis title	Immune response in Cohort 1
Comparison groups	Cohort 1 (7.5_Full MF59) v Cohort 1 (3.75_Half MF59)
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	4

Statistical analysis title	Immune response in Cohort 2
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (7.5_Full MF59)
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Immune response in Cohort 2
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	24

Statistical analysis title	Immune response in Cohort 2
Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	25

Statistical analysis title	Immune response in Cohort 3
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (7.5Full MF59)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Immune response in Cohort 3
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	26

Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	41

Statistical analysis title	Immune response in Cohort 3
Comparison groups	Cohort 3 (7.5Full MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	26
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	41

Statistical analysis title	Immune response in Cohort 4
Comparison groups	Cohort 4 (3.75_Half MF59) v Cohort 4 (7.5_Full MF59)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	5

Primary: Percentage of subjects achieving HI titers $\geq 1:40$ against A/H1N1 Strain.

End point title	Percentage of subjects achieving HI titers $\geq 1:40$ against A/H1N1 Strain.
-----------------	---

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving HI titers $\geq 1:40$ against A/H1N1 strain, 3 weeks after receiving 2 doses of vaccination according to CHMP criterion. There are no predefined CHMP criteria for the pediatric population however, the criterion is met if the percentage of subjects achieving HI antibody titer $\geq 1:40$ is $>70\%$ (at day 43).

End point type	Primary
----------------	---------

End point timeframe:

Day 1 and Day 43

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	70	66	60
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	14 (7 to 25)	17 (9 to 28)	12 (5 to 22)	18 (10 to 30)
Day 43	100 (94 to 100)	100 (95 to 100)	100 (95 to 100)	100 (94 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half)	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	60	58	31
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	24 (11 to 41)	18 (10 to 30)	24 (14 to 37)	26 (12 to 45)
Day 43	91 (76 to 98)	100 (94 to 100)	100 (94 to 100)	81 (63 to 93)

End point values	Cohort 4 (3.75_Half)	Cohort 4 (7.5_Full)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	22 (12 to 35)	22 (12 to 37)		
Day 43	98 (90 to 100)	100 (93 to 100)		

Statistical analyses

Statistical analysis title	Immune response in Cohort 1
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 1 (3.75_Half MF59) v Cohort 1 (7.5_Full MF59)

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Immune response in Cohort 2
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (7.5_Full MF59)
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Immune response in Cohort 2
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	18

Statistical analysis title	Immune response in Cohort 2
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	18

Statistical analysis title

Immune response in Cohort 3

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (7.5Full MF59)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title

Immune response in Cohort 3

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	19

Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	33

Statistical analysis title	Immune response in Cohort 3
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (7.5Full MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	33

Statistical analysis title	Immune response in Cohort 4
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 4 (3.75_Half MF59) v Cohort 4 (7.5_Full MF59)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	2

Primary: Geometric mean Ratios against A/H1N1 strain following 2-dose vaccination schedule as determined by HI assay

End point title	Geometric mean Ratios against A/H1N1 strain following 2-dose vaccination schedule as determined by HI assay
-----------------	---

End point description:

Immunogenicity was measured in terms of geometric mean ratios. The ratio of postvaccination to prevaccination HI GMTs, 3 weeks after second vaccination was reported.
There are no predefined CHMP criteria for the pediatric population however, the criterion is met if the geometric mean ratio (day 43/day 1) in HI antibody titer is >2.5.

End point type	Primary
----------------	---------

End point timeframe:

Day 1 and Day 43

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	70	66	60
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 43/Day 1	53 (34 to 84)	90 (58 to 142)	88 (56 to 138)	81 (50 to 132)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	60	58	31
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 43/Day 1	20 (11 to 35)	91 (51 to 162)	80 (44 to 146)	12 (6.43 to 21)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 43/Day 1	79 (44 to 142)	121 (66 to 225)		

Statistical analyses

Statistical analysis title	Immune response in Cohort 1
----------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 1 (3.75_Half MF59) v Cohort 1 (7.5_Full MF59)
-------------------	--

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.92

Statistical analysis title	Immune response in Cohort 2
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (3.75_Half MF59)
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.75

Statistical analysis title	Immune response in Cohort 2
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	4.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.49
upper limit	7.81

Statistical analysis title	Immune response in Cohort 2
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	4.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.28
upper limit	7.31

Statistical analysis title	Immune response in Cohort 3
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (7.5Full MF59)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.82

Statistical analysis title	Immune response in Cohort 3
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (15_No MF59)

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	7.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.35
upper limit	14

Statistical analysis title	Immune response in Cohort 3
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (7.5Full MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	6.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.82
upper limit	12

Statistical analysis title	Immune response in Cohort 4
-----------------------------------	-----------------------------

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 4 (3.75_Half MF59) v Cohort 4 (7.5_Full MF59)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Vaccine Group Ratios
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.32

Primary: Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After Primary Vaccination

End point title	Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After Primary Vaccination ^[1]
-----------------	--

End point description:

Safety was assessed as the number of subjects who reported solicited local and systemic adverse events, 3 weeks after the primary course with H1N1sw monovalent vaccine

End point type	Primary
----------------	---------

End point timeframe:

From day 1 through day 7 after any vaccination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	80	78	77
Units: Number				
Ecchymosis	7	6	7	8
Erythema	11	9	16	20
Induration	10	12	6	4
Swelling	7	7	3	8
Pain	42	48	29	40
Tenderness	0	0	0	0
Chills	2	3	3	3
Malaise	8	10	12	10
Myalgia	12	17	6	10
Arthralgia	4	5	3	6
Headache	16	14	7	15
Sweating	1	1	1	2
Fatigue	14	19	21	13
Nausea	3	4	9	4
Sleepiness	0	0	0	0
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Irritability	0	0	0	0
Change in eating	0	0	0	0
Shivering	0	0	0	0
Unusual Crying	0	0	0	0
Fever (≥38°C)	2	2	3	3
Temp (°C) ≥40.0°C	0	0	0	0
Stayed Home	3	3	4	6
Analg. Antipyr.	4	10	10	9

End point values	Cohort 2	Cohort 3 (3.75)	Cohort 3 (7.5)	Cohort 3
------------------	----------	-----------------	----------------	----------

	(15_No MF59)	_Half MF59)	Full MF59)	(15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	75	73	37
Units: Number				
Ecchymosis	4	8	7	2
Erythema	5	21	18	7
Induration	4	4	8	2
Swelling	3	3	2	1
Pain	10	0	0	0
Tenderness	0	26	25	8
Chills	4	0	0	0
Malaise	4	0	0	0
Myalgia	3	0	0	0
Arthralgia	3	0	0	0
Headache	1	0	0	0
Sweating	3	0	0	0
Fatigue	8	0	0	0
Nausea	1	0	0	0
Sleepiness	0	29	21	11
Diarrhea	0	18	15	9
Vomiting	0	7	4	4
Irritability	0	21	21	10
Change in eating	0	18	14	6
Shivering	0	8	7	4
Unusual Crying	0	23	21	9
Fever ($\geq 38^{\circ}\text{C}$)	2	7	11	3
Temp ($^{\circ}\text{C}$) $\geq 40.0^{\circ}\text{C}$	0	0	0	0
Stayed Home	3	11	8	2
Analg. Antipyr.	5	11	14	8

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: Number				
Ecchymosis	3	2		
Erythema	15	18		
Induration	3	2		
Swelling	2	1		
Pain	0	0		
Tenderness	11	18		
Chills	0	0		
Malaise	0	0		
Myalgia	0	0		
Arthralgia	0	0		
Headache	0	0		
Sweating	0	0		
Fatigue	0	0		
Nausea	0	0		

Sleepiness	30	34		
Diarrhea	21	23		
Vomiting	10	11		
Irritability	22	20		
Change in eating	18	20		
Shivering	6	5		
Unusual Crying	26	24		
Fever ($\geq 38^{\circ}\text{C}$)	9	10		
Temp ($^{\circ}\text{C}$) $\geq 40.0^{\circ}\text{C}$	1	0		
Stayed Home	8	8		
Analg. Antipyr.	22	23		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After booster Vaccination

End point title	Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After booster Vaccination ^[2]
-----------------	--

End point description:

Safety was assessed as the number of subjects who reported solicited local and systemic adverse events following booster vaccination, 12 months (day 366) after the first dose of primary vaccination.

End point type	Primary
----------------	---------

End point timeframe:

From day 366 through day 373.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	27	48	52
Units: Number				
Ecchymosis	1	1	3	5
Erythema	5	5	17	15
Induration	6	5	9	14
Swelling	5	4	5	10
Pain	22	22	34	37
Tenderness	0	0	0	0
Chills	1	4	3	8
Malaise	7	4	8	9
Myalgia	10	11	9	16
Arthralgia	5	7	4	8
Headache	4	13	4	15
Sweating	2	7	3	3
Fatigue	7	7	10	10
Nausea	4	5	4	7
Sleepiness	0	0	0	0

Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Irritability	0	0	0	0
Change in eating habits	0	0	0	0
Shivering	0	0	0	0
Unusual Crying	0	0	0	0
Fever (≥ 38C)	1	1	3	6
temperature(<38°C)	25	26	45	46
temperature ≥40°C	0	0	0	0
Stayed home	3	2	6	9
Anti./Ana. Med	1	6	6	8

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half)	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	52	57	29
Units: Number				
Ecchymosis	3	5	5	1
Erythema	6	20	16	3
Induration	3	16	10	2
Swelling	3	12	7	2
Pain	16	0	0	0
Tenderness	0	25	23	10
Chills	1	0	0	0
Malaise	2	0	0	0
Myalgia	2	0	0	0
Arthralgia	2	0	0	0
Headache	4	0	0	0
Sweating	0	0	0	0
Fatigue	3	0	0	0
Nausea	3	0	0	0
Sleepiness	0	7	5	4
Diarrhea	0	4	5	2
Vomiting	0	2	6	1
Irritability	0	13	12	5
Change in eating habits	0	5	3	4
Shivering	0	2	4	2
Unusual Crying	0	11	10	5
Fever (≥ 38C)	0	6	11	2
temperature(<38°C)	25	46	46	27
temperature ≥40°C	0	0	0	0
Stayed home	1	6	5	1
Anti./Ana. Med	4	13	14	4

End point values	Cohort 4 (3.75_Half)	Cohort 4 (7.5_Full)		
-------------------------	-------------------------	------------------------	--	--

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Number				
Ecchymosis	4	4		
Erythema	14	15		
Induration	9	12		
Swelling	6	8		
Pain	0	0		
Tenderness	17	19		
Chills	0	0		
Malaise	0	0		
Myalgia	0	0		
Arthralgia	0	0		
Headache	0	0		
Sweating	0	0		
Fatigue	0	0		
Nausea	0	0		
Sleepiness	8	13		
Diarrhea	9	8		
Vomiting	3	6		
Irritability	14	17		
Change in eating habits	10	13		
Shivering	4	4		
Unusual Crying	16	13		
Fever ($\geq 38^{\circ}\text{C}$)	12	11		
temperature($<38^{\circ}\text{C}$)	38	38		
temperature $\geq 40^{\circ}\text{C}$	0	0		
Stayed home	6	8		
Anti./Ana. Med	15	20		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Unsolicited Adverse Events after primary and booster vaccination.

End point title	Number of Subjects Reporting Unsolicited Adverse Events after primary and booster vaccination. ^[3]
-----------------	---

End point description:

Safety was assessed as the number of subjects who reported unsolicited adverse events after primary vaccination and following booster vaccination, 12 months (day 366) after the first dose of primary vaccination. For subjects aged <9 years of age at the time of booster received a second dose of seasonal vaccine on day 387.

All AEs were collected from day 1 to day 43 after primary vaccination, from day 366 through day 387 after vaccination and day 387 to day 546 for subjects who receive second dose of seasonal vaccine.

End point type	Primary
----------------	---------

End point timeframe:

Day 1 through day 43, day 366 through day 387, day 387 through day 546.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	80	77	77
Units: Number				
Any AE (Primary Vaccination)	27	30	36	32
Atleast Possibly Related AEs (Primary Vaccination)	5	15	8	9
Any AE N=84,85,78,82,38,63,68,35,68,62	4	1	12	10
Atleast Possibly AEN=84,85,78,82,38,63,68,35,68,62	1	0	2	2
Any AE N= 26,27,48,51,25,52,57,28,47,47	0	0	0	0
Atleast Possibly AEN=26,27,48,51,25,52,57,28,47,47	0	0	0	0

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	75	73	37
Units: Number				
Any AE (Primary Vaccination)	17	45	42	19
Atleast Possibly Related AEs (Primary Vaccination)	4	8	6	2
Any AE N=84,85,78,82,38,63,68,35,68,62	4	19	14	7
Atleast Possibly AEN=84,85,78,82,38,63,68,35,68,62	1	4	2	0
Any AE N= 26,27,48,51,25,52,57,28,47,47	0	0	0	0
Atleast Possibly AEN=26,27,48,51,25,52,57,28,47,47	0	0	0	0

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: Number				
Any AE (Primary Vaccination)	43	43		
Atleast Possibly Related AEs (Primary Vaccination)	11	12		
Any AE N=84,85,78,82,38,63,68,35,68,62	18	17		
Atleast Possibly AEN=84,85,78,82,38,63,68,35,68,62	5	2		

Any AE N= 26,27,48,51,25,52,57,28,47,47	0	0		
Atleast Possibly AEN=26,27,48,51,25,52,57,28,47,47	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Unsolicited Adverse Events

End point title	Number of Subjects Reporting Unsolicited Adverse Events ^[4]
-----------------	--

End point description:

Safety was assessed as the number of subjects who reported unsolicited adverse events. For subjects aged <9 years of age at the time of vaccination received a second dose of a seasonal vaccine on day 387.

SAEs, new onset of chronic diseases, AEs leading to withdrawal from the study were collected from day 1 to day 546 following 2-dose vaccination H1N1sw monovalent vaccine

End point type	Primary
----------------	---------

End point timeframe:

All AEs, SAEs, NOCDs, AEs leading to withdrawal-were collected through day 1 to day 546

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	80	77	77
Units: Numbers				
Any SAEs	6	3	3	4
At least possibly related SAEs	0	0	0	0
AEs leading to discontinuation	0	0	0	0
New onset of chronic disease	1	2	2	3

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half)	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	75	73	37
Units: Numbers				
Any SAEs	2	7	3	2
At least possibly related SAEs	0	0	0	0
AEs leading to discontinuation	0	1	0	0
New onset of chronic disease	1	1	1	1

End point values	Cohort 4 (3.75)	Cohort 4 (7.5)		
------------------	-----------------	----------------	--	--

	_Half MF59)	_Full MF59)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: Numbers				
Any SAEs	8	6		
At least possibly related SAEs	0	0		
AEs leading to discontinuation	2	1		
New onset of chronic disease	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving seroconversion against A/H1N1 Strain following a booster dose as measured by hemagglutination inhibition (HI) assay

End point title	Percentage of subjects achieving seroconversion against A/H1N1 Strain following a booster dose as measured by hemagglutination inhibition (HI) assay
-----------------	--

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving seroconversion or significant increase in HI titer against the A/H1N1 strain, after a booster dose with aTIV, administered 12 months after primary vaccination according to CHMP criterion.

At least one CHMP criterion as assessed three weeks after the booster dose should be met within each age cohort to fulfill regulatory requirements.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 387 (3 weeks post booster vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	36	37
Units: Percentages of subjects				
number (confidence interval 95%)	83 (61 to 95)	61 (39 to 80)	92 (78 to 98)	95 (82 to 99)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	44	42	23
Units: Percentages of subjects				
number (confidence interval 95%)	95 (77 to 100)	80 (65 to 90)	86 (71 to 95)	78 (56 to 93)

End point values	Cohort 4 (3.75_Half)	Cohort 4 (7.5_Full)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: Percentages of subjects				
number (confidence interval 95%)	81 (61 to 93)	77 (58 to 90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving HI titers $\geq 1:40$ against A/H1N1 Strain following a booster dose.

End point title	Percentage of subjects achieving HI titers $\geq 1:40$ against A/H1N1 Strain following a booster dose.
-----------------	--

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving HI titers $\geq 1:40$ against A/H1N1 strain after a booster dose with aTIV, administered 12 months after primary vaccination according to CHMP criterion.

At least one CHMP criterion as assessed three weeks after the booster dose should be met within each age cohort to fulfill regulatory requirement

End point type	Secondary
End point timeframe:	
Day 366 and Day 387	

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	27	46	44
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 366	96 (80 to 100)	100 (87 to 100)	85 (71 to 94)	100 (92 to 100)
Day 387 (N=23,23,36,37,22,44,42,23,26,30)	100 (85 to 100)	100 (85 to 100)	100 (90 to 100)	100 (91 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half)	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	48	54	26
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 366	64 (43 to 82)	98 (89 to 100)	98 (90 to 100)	62 (41 to 80)
Day 387 (N=23,23,36,37,22,44,42,23,26,30)	100 (85 to 100)	100 (92 to 100)	100 (92 to 100)	100 (85 to 100)

End point values	Cohort 4 (3.75_Half)	Cohort 4 (7.5_Full)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 366	95 (82 to 99)	100 (90 to 100)		
Day 387 (N=23,23,36,37,22,44,42,23,26,30)	100 (87 to 100)	100 (88 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean Ratios against A/H1N1 strain following a booster dose as determined by HI assay.

End point title	Geometric mean Ratios against A/H1N1 strain following a booster dose as determined by HI assay.
End point description:	
Immunogenicity was measured in terms of geometric mean ratios. The ratio of postvaccination to prevaccination HI GMTs after a booster dose with aTIV, administered 12 months after primary vaccination according to CHMP criterion was assessed	
End point type	Secondary
End point timeframe:	
Day 366 and Day 387	

End point values	Cohort 1 (3.75_Half)	Cohort 1 (7.5_Full)	Cohort 2 (3.75_Half)	Cohort 2 (7.5_Full)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	36	37
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 387/Day 366	9.52 (4.57 to 20)	5.28 (2.48 to 11)	18 (12 to 29)	13 (8.3 to 19)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half)	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	44	42	23
Units: Ratios				
geometric mean (confidence interval 95%)				

Day 387/Day 366	17 (10 to 28)	12 (5.82 to 24)	9.14 (4.5 to 19)	31 (15 to 64)
-----------------	---------------	-----------------	------------------	---------------

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 387/Day 366	14 (8.43 to 24)	8.11 (5.03 to 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean titers against A/H1N1 strain as determined by HI assay in pooled population

End point title	Geometric mean titers against A/H1N1 strain as determined by HI assay in pooled population
-----------------	--

End point description:

Immunogenicity was measured in terms of geometric mean titers against A/H1N1 strain, 3 weeks after second vaccination in pooled children population

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 and Day 43

End point values	Per protocol set- Day 43 All Cohorts (3.75_Half	Per protocol set- Day 43 All Cohorts (7.5_Full		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	246	237		
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	11 (7.78 to 15)	12 (9 to 17)		
Day 43	871 (711 to 1067)	1213 (987 to 1490)		

Statistical analyses

Statistical analysis title	Difference in HI GMTs of half and full dose MF59
----------------------------	--

Statistical analysis description:

To demonstrate the non-inferiority of immune response in terms of GMTs in subjects receiving 3.75 HA and half MF59, versus subjects receiving 7.5 HA and full MF59, 3 weeks after second vaccination

Comparison groups	Per protocol set- Day 43 All Cohorts (3.75_Half MF59) v Per protocol set- Day 43 All Cohorts (7.5_Full MF59)
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
Method	ANOVA
Parameter estimate	Vaccine Group ratios
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.86

Notes:

[5] - Non-inferiority will be concluded if the lower limit of the two sided 95% CI for the between group difference (3.75_Half MF59-7.5_Full MF59) in terms of post-immunization GMTs (at day 43) is higher or equal to 0.5.

If the hypothesis above can be rejected the same non-inferiority hypothesis were to be tested using a non-inferiority margin of 0.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 546

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.0
--------------------	------

Reporting groups

Reporting group title	Cohort 1 (3.75_Half MF59)
-----------------------	---------------------------

Reporting group description:

Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).

Reporting group title	Cohort 1 (7.5_Full MF59)
-----------------------	--------------------------

Reporting group description:

Subjects aged 9 to 17 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).

Reporting group title	Cohort 2 (3.75_Half MF59)
-----------------------	---------------------------

Reporting group description:

Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 2 (7.5_Full MF59)
-----------------------	--------------------------

Reporting group description:

Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 2 (15_No MF59)
-----------------------	-----------------------

Reporting group description:

Subjects aged 3 to 8 years received 2 doses of H1N1 vaccine (15mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 3 (3.75_Half MF59)
-----------------------	---------------------------

Reporting group description:

Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 3 (7.5Full MF59)
-----------------------	-------------------------

Reporting group description:

Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 3 (15_No MF59)
-----------------------	-----------------------

Reporting group description:

Subjects aged 12 to 35 months received 2 doses of H1N1 vaccine (1.5mcg HA + no MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 4 (3.75_Half MF59)
-----------------------	---------------------------

Reporting group description:

Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (3.75mcg HA + half MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 4 (7.5_Full MF59)
-----------------------	--------------------------

Reporting group description:

Subjects aged 6 to 11 months received 2 doses of H1N1 vaccine (7.5mcg HA + full MF59) administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Serious adverse events	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 94 (6.38%)	3 / 95 (3.16%)	3 / 89 (3.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
PNEUMONIA VIRAL			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATELLA FRACTURE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACCIDENTAL EXPOSURE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACE INJURY			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			

subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKULL FRACTURE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
TONSILLAR HYPERTROPHY			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ADENOTONSILLECTOMY			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CIRCUMCISION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
FEBRILE CONVULSION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			

subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOOCHEZIA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ADENOIDAL HYPERTROPHY			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	2 / 89 (2.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ABNORMAL BEHAVIOUR			
subjects affected / exposed	1 / 94 (1.06%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	1 / 94 (1.06%)	1 / 95 (1.05%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CHRONIC TONSILLITIS			
subjects affected / exposed	1 / 94 (1.06%)	1 / 95 (1.05%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	2 / 94 (2.13%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALPINGITIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 95 (1.05%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIOLITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS ADENOVIRUS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHARYNGITIS			

subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AMOEBIIC DYSENTERY			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 87 (4.60%)	2 / 44 (4.55%)	7 / 83 (8.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events			
Investigations			
PNEUMONIA VIRAL			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATELLA FRACTURE			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACCIDENTAL EXPOSURE			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACE INJURY			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKULL FRACTURE			

subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
TONSILLAR HYPERTROPHY			
subjects affected / exposed	1 / 87 (1.15%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ADENOTONSILLECTOMY			
subjects affected / exposed	1 / 87 (1.15%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CIRCUMCISION			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
FEBRILE CONVULSION			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 87 (0.00%)	1 / 44 (2.27%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHYZIA			

subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ADENOIDAL HYPERTROPHY			
subjects affected / exposed	1 / 87 (1.15%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ABNORMAL BEHAVIOUR			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC TONSILLITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GASTROENTERITIS			
subjects affected / exposed	2 / 87 (2.30%)	1 / 44 (2.27%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALPINGITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 87 (1.15%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	1 / 87 (1.15%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIOLITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS ADENOVIRUS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHARYNGITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AMOEBIC DYSENTERY			

subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events			
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 81 (4.94%)	2 / 42 (4.76%)	8 / 81 (9.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
PNEUMONIA VIRAL			

subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATELLA FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACCIDENTAL EXPOSURE			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACE INJURY			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKULL FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

TONSILLAR HYPERTROPHY			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ADENOTONSILLECTOMY			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CIRCUMCISION			
subjects affected / exposed	1 / 81 (1.23%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
FEBRILE CONVULSION			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 81 (0.00%)	1 / 42 (2.38%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHESIA			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ADENOIDAL HYPERTROPHY			

subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ABNORMAL BEHAVIOUR			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC TONSILLITIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALPINGITIS			

subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIOLITIS			
subjects affected / exposed	0 / 81 (0.00%)	1 / 42 (2.38%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS ADENOVIRUS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHARYNGITIS			
subjects affected / exposed	1 / 81 (1.23%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AMOEBCIC DYSENTERY			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	4 / 81 (4.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			

subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4 (7.5_Full MF59)		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 81 (7.41%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
PNEUMONIA VIRAL			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			

subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PATELLA FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACCIDENTAL EXPOSURE			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
FACE INJURY			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
FALL			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SKULL FRACTURE			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
TONSILLAR HYPERTROPHY			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			

ADENOTONSILLECTOMY			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CIRCUMCISION			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
FEBRILE CONVULSION			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DIARRHOEA			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HAEMATOCHESIA			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
ADENOIDAL HYPERTROPHY			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ASTHMA			

subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
ABNORMAL BEHAVIOUR			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CHRONIC TONSILLITIS			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SALPINGITIS			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRONCHIOLITIS				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTROENTERITIS ADENOVIRUS				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PHARYNGITIS				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
AMOEBIC DYSENTERY				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRONCHOPNEUMONIA				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OTITIS MEDIA				

subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 94 (70.21%)	69 / 95 (72.63%)	68 / 89 (76.40%)
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 94 (31.91%)	34 / 95 (35.79%)	14 / 89 (15.73%)
occurrences (all)	45	49	22
Somnolence			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 94 (5.32%)	7 / 95 (7.37%)	10 / 89 (11.24%)
occurrences (all)	6	9	10
Crying			

subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0	0 / 95 (0.00%) 0	0 / 89 (0.00%) 0
Fatigue			
subjects affected / exposed occurrences (all)	25 / 94 (26.60%) 36	27 / 95 (28.42%) 37	29 / 89 (32.58%) 43
Injection Site Erythema			
subjects affected / exposed occurrences (all)	21 / 94 (22.34%) 27	22 / 95 (23.16%) 28	37 / 89 (41.57%) 65
Injection Site Haemorrhage			
subjects affected / exposed occurrences (all)	10 / 94 (10.64%) 12	9 / 95 (9.47%) 12	12 / 89 (13.48%) 14
Injection Site Induration			
subjects affected / exposed occurrences (all)	18 / 94 (19.15%) 26	21 / 95 (22.11%) 24	18 / 89 (20.22%) 23
Injection Site Pain			
subjects affected / exposed occurrences (all)	54 / 94 (57.45%) 101	60 / 95 (63.16%) 114	55 / 89 (61.80%) 98
Injection Site Swelling			
subjects affected / exposed occurrences (all)	13 / 94 (13.83%) 16	14 / 95 (14.74%) 16	11 / 89 (12.36%) 17
Pyrexia			
subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 7	6 / 95 (6.32%) 6	17 / 89 (19.10%) 27
Malaise			
subjects affected / exposed occurrences (all)	19 / 94 (20.21%) 23	15 / 95 (15.79%) 21	22 / 89 (24.72%) 26
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0	2 / 95 (2.11%) 2	2 / 89 (2.25%) 2
Nausea			
subjects affected / exposed occurrences (all)	13 / 94 (13.83%) 13	14 / 95 (14.74%) 19	18 / 89 (20.22%) 21
Vomiting			
subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1	1 / 95 (1.05%) 1	1 / 89 (1.12%) 1

Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 94 (3.19%) 3	3 / 95 (3.16%) 3	7 / 89 (7.87%) 8
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	4 / 94 (4.26%) 5	8 / 95 (8.42%) 9	4 / 89 (4.49%) 8
Psychiatric disorders Irritability subjects affected / exposed occurrences (all) Eating Disorder subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1 0 / 94 (0.00%) 0	1 / 95 (1.05%) 1 0 / 95 (0.00%) 0	0 / 89 (0.00%) 0 0 / 89 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	12 / 94 (12.77%) 14 24 / 94 (25.53%) 31	13 / 95 (13.68%) 16 26 / 95 (27.37%) 39	8 / 89 (8.99%) 10 15 / 89 (16.85%) 20
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Ear Infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis	2 / 94 (2.13%) 2 0 / 94 (0.00%) 0 0 / 94 (0.00%) 0 0 / 94 (0.00%) 0	0 / 95 (0.00%) 0 0 / 95 (0.00%) 0 0 / 95 (0.00%) 0 0 / 95 (0.00%) 0	8 / 89 (8.99%) 9 0 / 89 (0.00%) 0 1 / 89 (1.12%) 1 4 / 89 (4.49%) 4

subjects affected / exposed	6 / 94 (6.38%)	5 / 95 (5.26%)	12 / 89 (13.48%)
occurrences (all)	6	5	12
Pharyngitis			
subjects affected / exposed	3 / 94 (3.19%)	0 / 95 (0.00%)	2 / 89 (2.25%)
occurrences (all)	3	0	2
Rhinitis			
subjects affected / exposed	5 / 94 (5.32%)	2 / 95 (2.11%)	0 / 89 (0.00%)
occurrences (all)	5	2	2
Varicella			
subjects affected / exposed	0 / 94 (0.00%)	0 / 95 (0.00%)	0 / 89 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 87 (81.61%)	31 / 44 (70.45%)	77 / 83 (92.77%)
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 87 (28.74%)	7 / 44 (15.91%)	1 / 83 (1.20%)
occurrences (all)	48	8	1
Somnolence			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	39 / 83 (46.99%)
occurrences (all)	0	0	72
General disorders and administration site conditions			
Chills			
subjects affected / exposed	13 / 87 (14.94%)	5 / 44 (11.36%)	15 / 83 (18.07%)
occurrences (all)	18	7	18
Crying			
subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	35 / 83 (42.17%)
occurrences (all)	0	0	58
Fatigue			
subjects affected / exposed	28 / 87 (32.18%)	12 / 44 (27.27%)	0 / 83 (0.00%)
occurrences (all)	47	17	0
Injection Site Erythema			
subjects affected / exposed	40 / 87 (45.98%)	12 / 44 (27.27%)	39 / 83 (46.99%)
occurrences (all)	61	18	72
Injection Site Haemorrhage			

subjects affected / exposed	14 / 87 (16.09%)	8 / 44 (18.18%)	15 / 83 (18.07%)
occurrences (all)	19	10	20
Injection Site Induration			
subjects affected / exposed	22 / 87 (25.29%)	8 / 44 (18.18%)	29 / 83 (34.94%)
occurrences (all)	32	8	42
Injection Site Pain			
subjects affected / exposed	57 / 87 (65.52%)	23 / 44 (52.27%)	46 / 83 (55.42%)
occurrences (all)	129	44	86
Injection Site Swelling			
subjects affected / exposed	19 / 87 (21.84%)	7 / 44 (15.91%)	22 / 83 (26.51%)
occurrences (all)	29	8	32
Pyrexia			
subjects affected / exposed	12 / 87 (13.79%)	7 / 44 (15.91%)	31 / 83 (37.35%)
occurrences (all)	20	11	41
Malaise			
subjects affected / exposed	19 / 87 (21.84%)	8 / 44 (18.18%)	1 / 83 (1.20%)
occurrences (all)	31	8	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 87 (3.45%)	0 / 44 (0.00%)	26 / 83 (31.33%)
occurrences (all)	3	0	48
Nausea			
subjects affected / exposed	12 / 87 (13.79%)	5 / 44 (11.36%)	1 / 83 (1.20%)
occurrences (all)	20	6	1
Vomiting			
subjects affected / exposed	2 / 87 (2.30%)	1 / 44 (2.27%)	16 / 83 (19.28%)
occurrences (all)	2	1	20
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 87 (11.49%)	4 / 44 (9.09%)	6 / 83 (7.23%)
occurrences (all)	12	4	6
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	8 / 87 (9.20%)	4 / 44 (9.09%)	0 / 83 (0.00%)
occurrences (all)	11	5	0
Psychiatric disorders			

Irritability subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 44 (0.00%) 0	38 / 83 (45.78%) 60
Eating Disorder subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 44 (0.00%) 0	33 / 83 (39.76%) 52
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	18 / 87 (20.69%) 26	6 / 44 (13.64%) 6	0 / 83 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	25 / 87 (28.74%) 40	4 / 44 (9.09%) 5	0 / 83 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	3 / 44 (6.82%) 4	10 / 83 (12.05%) 12
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 44 (0.00%) 0	5 / 83 (6.02%) 5
Ear Infection subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 44 (0.00%) 0	5 / 83 (6.02%) 5
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	1 / 44 (2.27%) 1	6 / 83 (7.23%) 6
Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 87 (9.20%) 11	3 / 44 (6.82%) 3	27 / 83 (32.53%) 36
Pharyngitis subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	0 / 44 (0.00%) 0	7 / 83 (8.43%) 7
Rhinitis subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 4	3 / 44 (6.82%) 3	2 / 83 (2.41%) 2
Varicella			

subjects affected / exposed	0 / 87 (0.00%)	0 / 44 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 3 (7.5Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 81 (93.83%)	37 / 42 (88.10%)	76 / 81 (93.83%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 81 (1.23%)	1 / 42 (2.38%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	28 / 81 (34.57%)	19 / 42 (45.24%)	34 / 81 (41.98%)
occurrences (all)	43	36	68
General disorders and administration site conditions			
Chills			
subjects affected / exposed	12 / 81 (14.81%)	7 / 42 (16.67%)	11 / 81 (13.58%)
occurrences (all)	13	10	15
Crying			
subjects affected / exposed	31 / 81 (38.27%)	12 / 42 (28.57%)	38 / 81 (46.91%)
occurrences (all)	53	27	74
Fatigue			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Injection Site Erythema			
subjects affected / exposed	39 / 81 (48.15%)	15 / 42 (35.71%)	36 / 81 (44.44%)
occurrences (all)	66	23	62
Injection Site Haemorrhage			
subjects affected / exposed	18 / 81 (22.22%)	5 / 42 (11.90%)	11 / 81 (13.58%)
occurrences (all)	24	7	14
Injection Site Induration			
subjects affected / exposed	27 / 81 (33.33%)	5 / 42 (11.90%)	18 / 81 (22.22%)
occurrences (all)	36	6	29
Injection Site Pain			
subjects affected / exposed	46 / 81 (56.79%)	21 / 42 (50.00%)	37 / 81 (45.68%)
occurrences (all)	85	36	64
Injection Site Swelling			

subjects affected / exposed occurrences (all)	14 / 81 (17.28%) 15	5 / 42 (11.90%) 7	18 / 81 (22.22%) 23
Pyrexia subjects affected / exposed occurrences (all)	36 / 81 (44.44%) 53	11 / 42 (26.19%) 18	30 / 81 (37.04%) 46
Malaise subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 42 (0.00%) 0	0 / 81 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	26 / 81 (32.10%) 42	12 / 42 (28.57%) 19	32 / 81 (39.51%) 68
Nausea subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 42 (0.00%) 0	0 / 81 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	16 / 81 (19.75%) 17	8 / 42 (19.05%) 10	20 / 81 (24.69%) 33
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	4 / 42 (9.52%) 4	4 / 81 (4.94%) 4
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 42 (0.00%) 0	1 / 81 (1.23%) 1
Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	30 / 81 (37.04%) 54	14 / 42 (33.33%) 30	32 / 81 (39.51%) 58
Eating Disorder subjects affected / exposed occurrences (all)	23 / 81 (28.40%) 36	14 / 42 (33.33%) 20	31 / 81 (38.27%) 45
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 81 (11.11%)	6 / 42 (14.29%)	13 / 81 (16.05%)
occurrences (all)	10	6	21
Conjunctivitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 42 (2.38%)	4 / 81 (4.94%)
occurrences (all)	1	1	5
Ear Infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 42 (0.00%)	0 / 81 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	2 / 81 (2.47%)	1 / 42 (2.38%)	4 / 81 (4.94%)
occurrences (all)	2	2	4
Nasopharyngitis			
subjects affected / exposed	19 / 81 (23.46%)	14 / 42 (33.33%)	34 / 81 (41.98%)
occurrences (all)	28	19	51
Pharyngitis			
subjects affected / exposed	4 / 81 (4.94%)	0 / 42 (0.00%)	8 / 81 (9.88%)
occurrences (all)	4	0	8
Rhinitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 42 (0.00%)	6 / 81 (7.41%)
occurrences (all)	1	0	6
Varicella			
subjects affected / exposed	1 / 81 (1.23%)	2 / 42 (4.76%)	3 / 81 (3.70%)
occurrences (all)	2	3	1

Non-serious adverse events	Cohort 4 (7.5_Full MF59)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 81 (95.06%)		
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	48 / 81 (59.26%)		
occurrences (all)	76		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	10 / 81 (12.35%)		
occurrences (all)	13		
Crying			
subjects affected / exposed	41 / 81 (50.62%)		
occurrences (all)	71		
Fatigue			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Injection Site Erythema			
subjects affected / exposed	34 / 81 (41.98%)		
occurrences (all)	64		
Injection Site Haemorrhage			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	10		
Injection Site Induration			
subjects affected / exposed	21 / 81 (25.93%)		
occurrences (all)	29		
Injection Site Pain			
subjects affected / exposed	41 / 81 (50.62%)		
occurrences (all)	69		
Injection Site Swelling			
subjects affected / exposed	15 / 81 (18.52%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	38 / 81 (46.91%)		
occurrences (all)	65		
Malaise			

subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	38 / 81 (46.91%)		
occurrences (all)	69		
Nausea			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	23 / 81 (28.40%)		
occurrences (all)	33		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	0		
Psychiatric disorders			
Irritability			
subjects affected / exposed	38 / 81 (46.91%)		
occurrences (all)	69		
Eating Disorder			
subjects affected / exposed	35 / 81 (43.21%)		
occurrences (all)	55		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Bronchitis			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	10		
Conjunctivitis			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Ear Infection			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	28 / 81 (34.57%)		
occurrences (all)	38		
Pharyngitis			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	8		
Rhinitis			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	4		
Varicella			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2009	<ul style="list-style-type: none">•Subgroup analysis based on previous seasonal influenza vaccination was performed•Differences addressing within-group comparisons were not calculated for binary data due to the lack of appropriate validated standard software.•Center as qualitative factor was not included in the models for binary data as in a lot of instances algorithms do not converge or results highly depended on the choice of the "addcell" options in SAS proc catmod.•Center was included as qualitative factor only in models for normal distributed data to obtain adjusted estimates
23 November 2009	Four minor changes for further clarity (i.e.stopping rules, public disclosure of study results and clarification of exclusion criteria).
30 November 2009	To allow interim analyses if there is a request in public health interest
06 February 2010	To address the EMEA request, multivariate analysis of immunogenicity data was performed at day 22 and day 43. The description of multivariate analysis is in section 16.1.9.
07 November 2010	To address the change that the booster will be administered using the egg-derived, seasonal, trivalent MF59 adjuvanted vaccine Fluad.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported